

10/674727

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FILE 'REGISTRY' ENTERED AT 11:52:56 ON 31 OCT 2006

=> d his

FILE 'HCAPLUS' ENTERED AT 11:25:31 ON 31 OCT 2006
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SEL RN

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L3 STR
L4 7 S L3
L5 50 S L3 FUL
L6 7 S L5 AND L2
SAV L5 SPI727/A

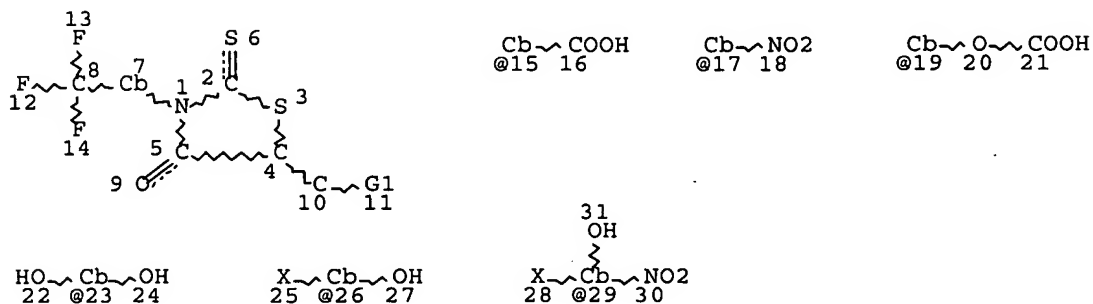
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L9 11 S L7 OR L8

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L10 0 S L5
L11 8 S L5 FUL
L12 6 S L11 NOT L9

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L13 0 S L5

=> d que 19

L2 13 SEA FILE=REGISTRY ABB=ON (121-44-8/BI OR 292174-08-4/B
I OR 301308-44-1/BI OR 303056-54-4/BI OR 307510-92-5/BI
OR 328250-71-1/BI OR 504-78-9/BI OR 50718-91-7/BI OR
535962-72-2/BI OR 619-66-9/BI OR 677027-74-6/BI OR
677027-75-7/BI OR 98-16-8/BI)
L3 STR



VAR G1=15/17/19/23/26/29
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 31

STEREO ATTRIBUTES: NONE

L5 50 SEA FILE=REGISTRY SSS FUL L3
L6 7 SEA FILE=REGISTRY ABB=ON L5 AND L2
L7 9 SEA FILE=HCAPLUS ABB=ON L6
L8 11 SEA FILE=HCAPLUS ABB=ON L5
L9 11 SEA FILE=HCAPLUS ABB=ON L7 OR L8

=> fil hcap
FILE 'HCAPLUS' ENTERED AT 11:53:09 ON 31 OCT 2006

=> d l9 1-11 ibib abs hitstr hitind

L9 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1134223 HCAPLUS Full-text

DOCUMENT NUMBER: 144:396

TITLE: A novel small molecule CFTR inhibitor
attenuates HCO₃⁻ secretion and duodenal ulcer
formation in rats

AUTHOR(S): Akiba, Yasutada; Jung, Michael; Ouk, Samedy;
Kaunitz, Jonathan D.

CORPORATE SOURCE: Department of Medicine, School of Medicine,
University of California, Los Angeles, CA, USA

SOURCE: American Journal of Physiology (2005), 289(4,
Pt. 1), G753-G759

CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

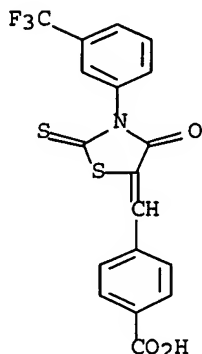
LANGUAGE: English

AB The cystic fibrosis (CF) transmembrane conductance regulator (CFTR) plays a crucial role in mediating duodenal bicarbonate (HCO₃⁻) secretion (DBS). Although impaired DBS is observed in CF mutant mice and in CF patients, which would predict increased ulcer susceptibility, duodenal injury is rarely observed in CF patients and is reduced in CF mutant mice. To explain this apparent paradox, we hypothesized that CFTR dysfunction increases cellular [HCO₃⁻] and buffering power. To further test this hypothesis, we examined the effect of a novel, potent, and highly selective CFTR inhibitor, CFTRinh-172, on DBS and duodenal ulceration in rats. DBS was measured in situ using a standard loop perfusion model with a pH stat under isoflurane anesthesia. Duodenal ulcers were induced in rats by cysteamine with or without CFTRinh-172 pretreatment 1 h before cysteamine. Superfusion of CFTRinh-172 (0.1-10 μM) over the duodenal mucosa had no effect on basal DBS but at 10 μM inhibited acid-induced DBS, suggesting that its effect was limited to CFTR activation. Acid-induced DBS was abolished at 1 and 3 h and was reduced 24 h after treatment with CFTRinh-172, although basal DBS was increased at 24 h. CFTRinh-172 treatment had no effect on gastric acid or HCO₃⁻ secretion. Duodenal ulcers were observed 24 h after cysteamine treatment but were reduced in CFTRinh-172-pretreated rats. CFTRinh-172 acutely produces CFTR dysfunction in rodents for up to 24 h. CFTR inhibition reduces acid-induced DBS but also prevents duodenal ulcer formation, supporting our hypothesis that intracellular HCO₃⁻ may be an important protective mechanism for duodenal epithelial cells.

IT 307510-92-5, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone
(CFTRh-172; novel small mol. CFTR inhibitor attenuates
bicarbonate secretion and duodenal ulcer formation in rats)

RN 307510-92-5 HCAPLUS

CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



CC 1-9 (Pharmacology)

Section cross-reference(s): 13, 14

IT 307510-92-5, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone
(CFTRh-172; novel small mol. CFTR inhibitor attenuates bicarbonate secretion and duodenal ulcer formation in rats)

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:108287 HCAPLUS Full-text

DOCUMENT NUMBER: 143:191261

TITLE: Predominant constitutive CFTR conductance in small airways

AUTHOR(S): Wang, Xiaofei; Lytle, Christian; Quinton, Paul M.

CORPORATE SOURCE: Dept. Prediatrics, Med. Sch., Univ. California, San Diego, San Diego, CA, USA

SOURCE: Respiratory Research (2005), 6(1), No pp. given

CODEN: RREEBZ; ISSN: 1465-993X

URL: <http://respiratory-research.com/content/pdf/1465-9921-6-7.pdf>

PUBLISHER: BioMed Central Ltd.

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Background: The pathol. hallmarks of chronic obstructive pulmonary disease (COPD) are inflammation of the small airways (bronchiolitis) and destruction of lung parenchyma (emphysema). These forms of disease arise from chronic prolonged infections, which are usually never present in the normal lung. Despite the fact that primary hygiene and defense of the airways presumably requires a well controlled fluid environment on the surface of the bronchiolar airway, very little is known of the fluid and electrolyte transport properties of airways of less than a few mm diameter. Methods: We introduce a novel approach to examine some of these properties in a preparation of minimally traumatized porcine bronchioles of about 1 mm diameter by microperfusing the intact bronchiole. Results: In bilateral isotonic NaCl Ringer solns., the spontaneous transepithelial potential (TEP; lumen to bath) of the bronchiole

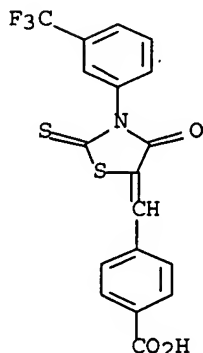
was small (mean±sem: -3± mV; n=25), but when gluconate replaced luminal Cl- the bionic Cl- diffusion potentials (-58±3 mV; n=25) were as large as -90 mV. TEP diffusion potentials from 2:1 NaCl dilution showed that epithelial Cl- permeability was at least 5 times greater than Na+ permeability. The anion selectivity sequence was similar to that of CFTR. The bionic TEP became more electroneg. with stimulation by luminal forskolin (5 µM)+IBMX (100 µM), ATP (100 µM), or adenosine (100 µM), but not by ionomycin. The TEP was partially inhibited by NPPB (100 µM), GlyH-101* (5-50 µM), and CFTRInh-172* (5 µM). RT-PCR gave identifying products for CFTR, α-, β-, and γ-ENaC and NKCC1. Antibodies to CFTR localized specifically to the epithelial cells lining the lumen of the small airways. Conclusion: These results indicate that the small airway of the pig is characterized by a constitutively active Cl- conductance that is most likely due to CFTR.

IT 307510-92-5

(anion conductance inhibitor CFTRInh-172 significantly depolarized transepithelial potential in pig bronchiole)

RN 307510-92-5 HCAPLUS

CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



CC 14-4 (Mammalian Pathological Biochemistry)

IT 307510-92-5

(anion conductance inhibitor CFTRInh-172 significantly depolarized transepithelial potential in pig bronchiole)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:37884 HCAPLUS Full-text

DOCUMENT NUMBER: 142:403893

TITLE: In vivo pharmacology and antidiarrheal efficacy of a thiazolidinone CFTR inhibitor in rodents

AUTHOR(S): Sonawane, N. D.; Muanprasat, Chatchai; Nagatani, Ray, Jr.; Song, Yuanlin; Verkman, A. S.

CORPORATE SOURCE: Departments of Medicine and Physiology, Cardiovascular Research Institute, University of California, San Francisco, CA, 94143-0521, USA

SOURCE: Journal of Pharmaceutical Sciences (2005),

94(1), 134-143

CODEN: JPMSAE; ISSN: 0022-3549

PUBLISHER:

Wiley-Liss, Inc.

DOCUMENT TYPE:

Journal

LANGUAGE:

English

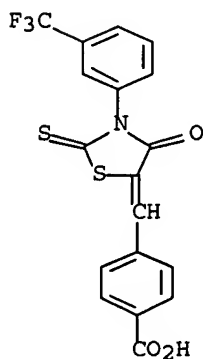
AB A small-mol. inhibitor of the cystic fibrosis transmembrane conductance regulator (CFTR), 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone (CFTRinh-172), reduces enterotoxin-induced intestinal fluid secretion in rodents. Here, we study CFTRinh-172 pharmacol. and antidiarrheal efficacy in rodents using ¹⁴C-labeled CFTRinh-172, liquid chromatog./mass spectrometry, and a closed intestinal loop model of fluid secretion. CFTRinh-172 was cleared primarily by renal glomerular filtration without chemical modification. CFTRinh-172 accumulated in liver within 5 min after i.v. infusion in mice, and was concentrated fivefold in bile over blood. At 30-240 min, CFTRinh-172 was found mainly in liver, intestine, and kidney, with little detectable in the brain, heart, skeletal muscle, or lung. Pharmacokinetic anal. in rats following i.v. bolus infusion showed a distribution volume of 770 mL with redistribution and elimination half-times of 0.14 h and 10.3 h, resp. CFTRinh-172 was stable in hepatic microsomes. Closed-loop studies in mice indicated that a single i.p. injection of 20 µg CFTRinh-172 inhibited fluid accumulation at 6 h after cholera toxin by >90% in duodenum and jejunum, .apprx.60% in ileum and <10% in colon. No toxicity was seen after high-dose CFTRinh-172 administration (3 mg/kg/day in two daily doses) in mice over the first 6 wk of life. The metabolic stability, enterohepatic recirculation, slow renal elimination, and intestinal accumulation of CFTRinh-172 account for its efficacy as an antidiarrheal.

IT 307510-92-5

(in vivo pharmacol. and antidiarrheal efficacy of a thiazolidinone CFTR inhibitor in rodents)

RN 307510-92-5 HCAPLUS

CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



CC 1-9 (Pharmacology)

IT 307510-92-5

(in vivo pharmacol. and antidiarrheal efficacy of a thiazolidinone CFTR inhibitor in rodents)

REFERENCE COUNT:

29

THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:671764 HCAPLUS Full-text

DOCUMENT NUMBER: 141:222260

TITLE: Effects of a new cystic fibrosis transmembrane conductance regulator inhibitor on Cl- conductance in human sweat ducts

AUTHOR(S): Wang, X. F.; Reddy, M. M.; Quinton, P. M.

CORPORATE SOURCE: Department of Pediatrics, University of California San Diego, La Jolla, CA, 92093-0831, USA

SOURCE: Experimental Physiology (2004), 89(4), 417-425

CODEN: EXPHEZ; ISSN: 0958-0670

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal

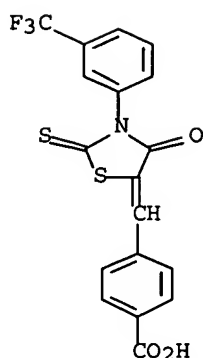
LANGUAGE: English

AB Effective and specific inhibition of the cystic fibrosis transmembrane conductance regulator (CFTR) Cl- channel in epithelia has long been needed to better understand the role of anion movements in fluid and electrolyte transport. Until now, available inhibitors have required high concns., usually in the millimolar or high micromolar range, to effect even an incomplete block of channel conductance. These inhibitors, including 5-nitro-2(3-phenylpropyl-amino)benzoate (NPPB), bumetamide, glibenclamide and DIDS, are also relatively non-specific. Recently a new anion channel inhibitor, a thiazolidinone derivative, termed CFTRInh-172 has been synthesized and introduced with apparently improved inhibitory properties as shown by effects on anion conductance expressed in cell lines and on secretion in vivo. Here, we assay the effect of this inhibitor on a purely salt absorbing native epithelial tissue, the freshly isolated microperfused human sweat duct, known for its inherently high expression of CFTR. We found that the inhibitor at a maximum dose limited by its aqueous solubility of 5 μ M partially blocked CFTR when applied to either surface of the membrane; however, it may be somewhat more effective from the cytosolic side (.apprx.70% inhibition). It may also partially inhibit Na+ conductance. The inhibition was relatively slow, with a half time for maximum effect of about 3 min, and showed very slow reversibility. Results also suggest that CFTR Cl- conductance (GCl) was blocked in both apical and basal membranes. The inhibitor appears to exert some effect on Na+ transport as well.

IT 307510-92-5, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone
(CFTRInh-172; effects of new cystic fibrosis transmembrane conductance regulator inhibitor on Cl- conductance in human sweat ducts)

RN 307510-92-5 HCAPLUS

CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



CC 13-2 (Mammalian Biochemistry)

Section cross-reference(s): 6

IT 307510-92-5, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone
(CFTRinh-172; effects of new cystic fibrosis transmembrane conductance regulator inhibitor on Cl⁻ conductance in human sweat ducts)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:506016 HCAPLUS Full-text

DOCUMENT NUMBER: 141:236485

TITLE: Synthesis and characterization of a small molecule CFTR chloride channel inhibitor

AUTHOR(S): He, Cheng-yan; Zhang, Heng-jun; Su, Zhong-min; Zhou, Jin-song; Yang, Hong; Ma, Tong-hui

CORPORATE SOURCE: Membrane Channel Research Laboratory, Northeast Normal University, Changchun, 130024, Peop. Rep. China

SOURCE: Chemical Research in Chinese Universities (2004), 20(3), 334-337

CODEN: CRCUED; ISSN: 1005-9040

PUBLISHER: Higher Education Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A thiazolidinone CFTR inhibitor (CFTRinh-172) was synthesized by a three-step procedure with trifluoromethylaniline as the starting material. The synthesized CFTR inhibitor was characterized structurally by ¹H-NMR and functionally in a CFTR-expressing cell line FRT/hCFTR/EYFP-H148Q by both fluorescent and electrophysiol. methods. A large amount (100 g) of high-quality small mol. thiazolidinone CFTR chloride channel inhibitor, CFTRinh-172, can be produced with this simple three-step synthetic procedure. The structure of the final product 2-thioxo-3-(3-trifluoromethylphenyl)-5-[4-carboxyphenyl-methylene]-4-thiazolidinone was confirmed by ¹H NMR. The overall yield was 58% with a purity over 99% as analyzed by HPLC. The synthesized CFTRinh-172 specifically inhibited CFTR chloride channel function in a cell-based fluorescence assay ($K_d \approx 1.5 \mu\text{mol/L}$) and in a Ussing chamber-based short-circuit current assay ($K_d \approx 0.2 \mu\text{mol/L}$), indicating better quality than that of the com. combinatorial compound. The synthesized inhibitor is nontoxic to cultured cells at a high concentration and to mouse at a high dose. The synthetic procedure developed here can be used to produce a large

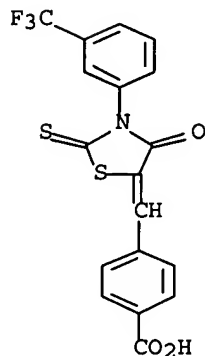
amount of the high-quality CFTRinh-172 suitable for antidiarrheal studies and for creation of cystic fibrosis models in large animals. The procedure can be used to synthesize radiolabeled CFTRinh-172 for in vivo pharmacokinetics studies.

IT 307510-92-5P

(synthesis and characterization of a small mol. CFTR chloride channel inhibitor)

RN 307510-92-5 HCAPLUS

CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



CC 1-12 (Pharmacology)

IT 307510-92-5P

(synthesis and characterization of a small mol. CFTR chloride channel inhibitor)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:290483 HCAPLUS Full-text

DOCUMENT NUMBER: 140:315071

TITLE: Thiazolidinone cystic fibrosis transmembrane conductance regulator protein inhibitors and pharmaceutical preps. for treatment of CFTR-mediated diseases and conditions

INVENTOR(S): Verkman, Alan; Ma, Tonghui

PATENT ASSIGNEE(S): The Regents of the University of California, USA

SOURCE: PCT Int. Appl., 78 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004028480	A2	20040408	WO 2003-US31005	2003 0930

WO 2004028480 A3 20040701
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES,
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,
MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ,
DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL,
PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG

US 2004063695 A1 20040401 US 2002-262573 2002
0930

CA 2500498 AA 20040408 CA 2003-2500498 2003
0930

AU 2003277162 A1 20040419 AU 2003-277162 2003
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US 2004235800 A1 20041125 US 2003-676727 2003
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EP 1549321 A2 20050706 EP 2003-798805 2003
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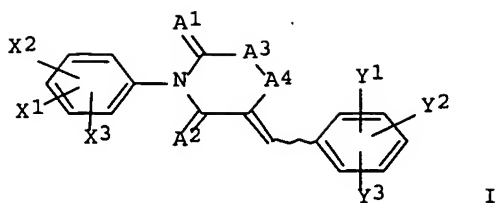
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0930

US 2002-509049P P 2002
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US 2003-480253P P 2003
0620

WO 2003-US31005 W 2003
0930

OTHER SOURCE(S): MARPAT 140:315071
GI



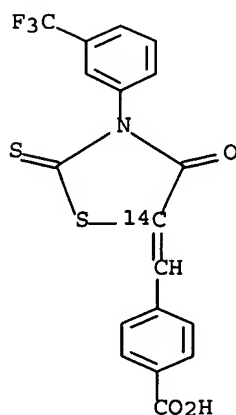
AB The invention discloses compns., pharmaceutical preps. and methods for inhibition of cystic fibrosis transmembrane conductance regulator protein (CFTR) that are useful for the study and treatment of CFTR-mediated diseases and conditions. The compns. and pharmaceutical preps. of the invention may comprise one or more thiazolidinone compds. I (X1-X3, Y1-Y3=H, organic group, halo, nitro, azo, OH, mercapto; A1, A2=O, S; A3=S, Se; A4= ≥ 1 C or heteroatom or is absent), and may addnl. comprise one or more pharmaceutically acceptable carriers, excipients and/or adjuvants. The methods of the invention comprise, in certain embodiments, administering to a patient suffering from a CFTR-mediated disease or condition, an efficacious amount of a thiazolidinone compound. In other embodiments the invention provides methods of inhibiting CFTR that comprise contacting cells in a subject with an effective amount of a thiazolidinone compound. In addition, the invention features a non-human animal model of CFTR-mediated disease which model is produced by administration of a thiazolidinone compound to a non-human animal in an amount sufficient to inhibit CFTR.

IT 677027-75-7P

(thiazolidinone cystic fibrosis transmembrane conductance regulator protein inhibitors and pharmaceutical preps. for treatment of CFTR-mediated diseases and conditions)

RN 677027-75-7 HCAPLUS

CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene-5- 14 C]methyl]- (9CI) (CA INDEX NAME)



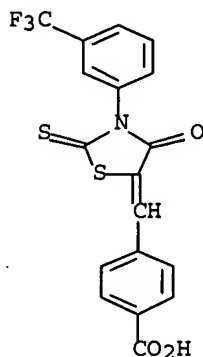
IT 307510-92-5P

(thiazolidinone cystic fibrosis transmembrane conductance regulator protein inhibitors and pharmaceutical preps. for

treatment of CFTR-mediated diseases and conditions)

RN 307510-92-5 HCAPLUS

CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinyldene]methyl]- (9CI) (CA INDEX NAME)



IT 292174-08-4, 3-[(3-Trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone

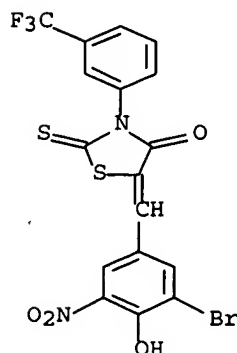
301308-44-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone

303056-54-4 328250-71-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone 535962-72-2

(thiazolidinone cystic fibrosis transmembrane conductance regulator protein inhibitors and pharmaceutical preps. for treatment of CFTR-mediated diseases and conditions)

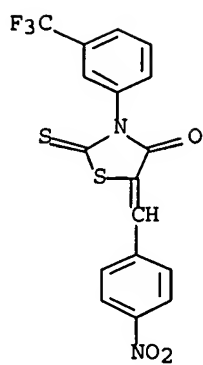
RN 292174-08-4 HCAPLUS

CN 4-Thiazolidinone, 5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



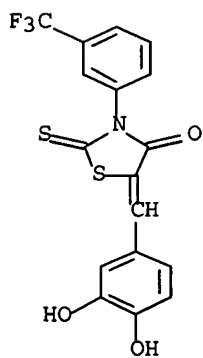
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CN 4-Thiazolidinone, 5-[(4-nitrophenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



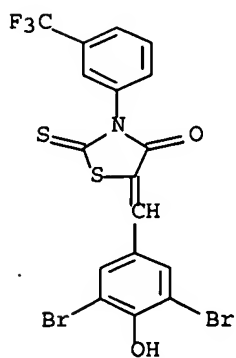
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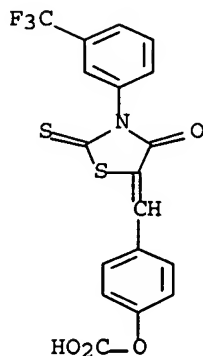


RN 328250-71-1 HCAPLUS

CN 4-Thiazolidinone, 5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 535962-72-2 HCAPLUS
CN 4-Thiazolidinone, 5-[[4-(carboxyoxymethyl)phenyl]methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



IC ICM A61K
CC 1-9 (Pharmacology)
Section cross-reference(s): 14, 28, 63
IT 677027-75-7P
(thiazolidinone cystic fibrosis transmembrane conductance regulator protein inhibitors and pharmaceutical preps. for treatment of CFTR-mediated diseases and conditions)
IT 307510-92-5P
(thiazolidinone cystic fibrosis transmembrane conductance regulator protein inhibitors and pharmaceutical preps. for treatment of CFTR-mediated diseases and conditions)
IT 504-78-9D, Thiazolidine, derivs. 292174-08-4,
3-[(3-Trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone
301308-44-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone
303056-54-4 328250-71-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone 535962-72-2
(thiazolidinone cystic fibrosis transmembrane conductance regulator protein inhibitors and pharmaceutical preps. for treatment of CFTR-mediated diseases and conditions)

L9 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:269861 HCAPLUS Full-text
DOCUMENT NUMBER: 140:247127
TITLE: Thiazolidinone compound cystic fibrosis transmembrane conductance regulator protein inhibitors, uses, and animal model of CFTR-mediated disease
INVENTOR(S): Verkman, Alan; Ma, Tonghui
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 22 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004063695	A1	20040401	US 2002-262573	2002 0930
CA 2500498	AA	20040408	CA 2003-2500498	2003 0930
WO 2004028480	A2	20040408	WO 2003-US31005	2003 0930
WO 2004028480	A3	20040701		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003277162	A1	20040419	AU 2003-277162	2003 0930
EP 1549321	A2	20050706	EP 2003-798805	2003 0930
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003014943	A	20050802	BR 2003-14943	2003 0930
CN 1684686	A	20051019	CN 2003-823366	2003 0930
JP 2006503853	T2	20060202	JP 2004-540305	2003 0930
PRIORITY APPLN. INFO.:				
			US 2002-262573	A 2002 0930
			US 2002-509049P	P 2002 0930
			US 2003-480253P	P 2003 0620
			WO 2003-US31005	W 2003 0930

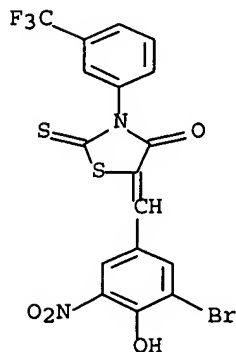
OTHER SOURCE(S): MARPAT 140:247127

AB The invention provides compns., pharmaceutical preps., and methods for inhibition of cystic fibrosis transmembrane conductance regulator protein (CFTR) that are useful for the study and treatment of CFTR-mediated diseases and conditions. The compns. and pharmaceutical preps. of the invention may comprise one or more thiazolidinone compds., and may addnl. comprise one or more pharmaceutically acceptable carriers, excipients and/or adjuvants. The methods of the invention comprise, in certain embodiments, administering to a patient suffering from a CFTR-mediated disease or condition, an efficacious amount of a thiazolidinone compound. In other embodiments the invention provides methods of inhibiting CFTR that comprise contacting cells in a subject with an effective amount of a thiazolidinone compound. In addition, the invention features a non-human animal model of CFTR-mediated disease which model is produced by administration of a thiazolidinone compound to a non-human animal in an amount sufficient to inhibit CFTR.

IT 292174-08-4, 3-[(3-Trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone
301308-44-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone
303056-54-4 307510-92-5, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone 328250-71-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone 535962-72-2,
3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyoxyphenyl)methylene]-2-thioxo-4-thiazolidinone
(thiazolidinone compound CFTR inhibitors, uses, and animal model of CFTR-mediated disease)

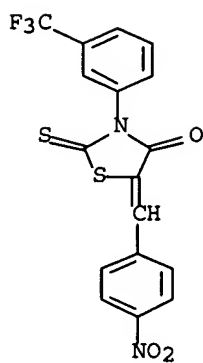
RN 292174-08-4 HCAPLUS

CN 4-Thiazolidinone, 5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



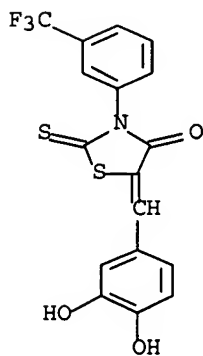
RN 301308-44-1 HCAPLUS

CN 4-Thiazolidinone, 5-[(4-nitrophenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



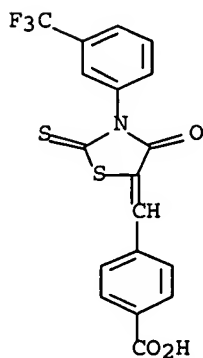
RN 303056-54-4 HCAPLUS

CN 4-Thiazolidinone, 5-[(3,4-dihydroxyphenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)

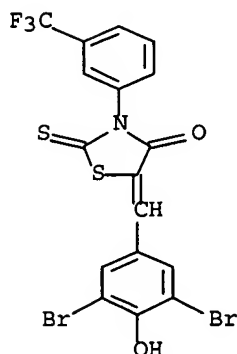


RN 307510-92-5 HCAPLUS

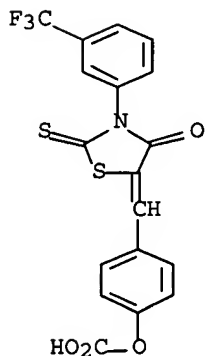
CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



RN 328250-71-1 HCAPLUS
 CN 4-Thiazolidinone, 5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 535962-72-2 HCAPLUS
 CN 4-Thiazolidinone, 5-[[4-(carboxyoxo)phenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



IC ICM A61K031-549
 INCL 514222500
 CC 1-12 (Pharmacology)
 Section cross-reference(s): 14, 63
 IT 141-84-4D, 2-Thioxo-4-thiazolidinone, derivs. 28600-65-9D,
 Thiazolidinone, derivs. 292174-08-4,
 3-[(3-Trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone
 301308-44-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone
 303056-54-4 307510-92-5, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone 328250-71-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone 535962-72-2,
 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyoxo)phenyl)methylene]-2-

thioxo-4-thiazolidinone

(thiazolidinone compound CFTR inhibitors, uses, and animal model
of CFTR-mediated disease)

L9 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:189841 HCAPLUS Full-text

DOCUMENT NUMBER: 141:254187

TITLE: Prevention of toxin-induced intestinal ion and
fluid secretion by a small-molecule CFTR
inhibitor

AUTHOR(S): Thiagarajah, Jay R.; Broadbent, Talmage;
Hsieh, Emily; Verkman, Alan S.

CORPORATE SOURCE: Departments of Medicine and Physiology,
Cardiovascular Research Institute, University
of California, San Francisco, CA, USA

SOURCE: Gastroenterology (2004), 126(2), 511-519
CODEN: GASTAB; ISSN: 0016-5085

PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal

LANGUAGE: English

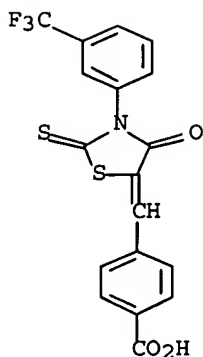
AB Background & Aims: The cystic fibrosis transmembrane conductance regulator
(CFTR) provides an important apical route for Cl⁻ secretion across intestinal
epithelia. A thiazolidinone-type CFTR blocker (CFTRinh-172) reduced cholera
toxin-induced fluid accumulation in mouse intestinal loops. Here, we
characterize the efficacy and pharmacodynamics of CFTRinh-172 in blocking cAMP
and cGMP induced Cl⁻/fluid secretion in rodent and human intestine. Methods &
Results: CFTRinh-172 inhibited cAMP and cGMP agonist induced short-circuit
current by >95% in T84 colonic epithelial cells (KI .apprx. 3 µmol/L) and in
mouse and human intestinal sheets (KI .apprx. 9 µmol/L). A single i.p.
injection of CFTRinh-172 (200 µg) blocked intestinal fluid secretion in a rat
closed-loop model by >90% for cholera toxin and >70% for STa Escherichia coli
toxin. In mice, CFTRinh-172 (20 µg) inhibited cholera toxin-induced
intestinal fluid secretion by 90% (persistence t_{1/2} .apprx. 10 h, KI .apprx. 5
µg) and STa toxin by 75% (KI .apprx. 10 µg). Tissue distribution and
pharmacokinetic studies indicated intestinal CFTRinh-172 accumulation
facilitated by enterohepatic circulation. An oral CFTRinh-172 preparation
reduced fluid secretion by >90% in a mouse open-loop cholera model.
Conclusions: A small mol. CFTR blocker markedly reduced intestinal ion and
fluid secretion caused by cAMP/cGMP-dependent bacterial enterotoxins. CFTR
inhibition may thus reduce fluid secretion in infectious secretory diarrheas.

IT 307510-92-5

(thiazolidinone-type CFTR blocker CFTRinh-172 reduced
intestinal ion and fluid secretion caused by
cAMP/cGMP-dependent bacterial enterotoxin in rodent and human
intestine without affecting intestinal fluid absorption)

RN 307510-92-5 HCAPLUS

CN Benzoic acid, 4-[[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-
thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



CC 1-9 (Pharmacology)

IT 307510-92-5

(thiazolidinone-type CFTR blocker CFTRinh-172 reduced intestinal ion and fluid secretion caused by cAMP/cGMP-dependent bacterial enterotoxin in rodent and human intestine without affecting intestinal fluid absorption)

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:94932 HCAPLUS Full-text

DOCUMENT NUMBER: 140:281314

TITLE: Altered channel gating mechanism for CFTR inhibition by a high-affinity thiazolidinone blocker

AUTHOR(S): Taddei, Alessandro; Folli, Chiara; Zegarra-Moran, Olga; Fanen, Pascale; Verkman, A. S.; Galletta, Luis J. V.

CORPORATE SOURCE: Laboratorio di Genetica Molecolare, Istituto Giannina Gaslini, Genoa, 16148, Italy

SOURCE: FEBS Letters (2004), 558(1-3), 52-56
CODEN: FEBLAL; ISSN: 0014-5793

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The thiazolidinone CFTRinh-172 was identified recently as a potent and selective blocker of the cystic fibrosis transmembrane conductance regulator (CFTR) Cl⁻ channel. Here, we characterized the CFTRinh-172 inhibition mechanism by patch-clamp and short-circuit anal. using cells stably expressing wild-type and mutant CFTRs. CFTRinh-172 did not alter CFTR unitary conductance (8 pS), but reduced open probability by >90% with $K_i \approx 0.6 \mu\text{M}$. This effect was due to increased mean channel closed time without changing mean channel open time. Short-circuit current expts. indicated similar CFTRinh-172 inhibitory potency ($K_i \approx 0.5 \mu\text{M}$) for inhibition of Cl⁻ current in wild-type, G551D, and G1349D CFTR; however, K_i was significantly reduced to $0.2 \mu\text{M}$ for $\Delta F508$ CFTR. Our studies provide evidence for CFTR inhibition by CFTRinh-172 by a mechanism involving altered CFTR gating.

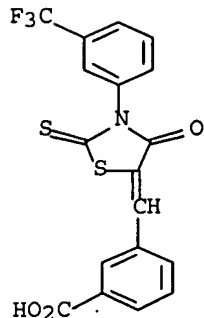
IT 432526-28-8

(altered channel gating mechanism for CFTR inhibition by high-affinity thiazolidinone blocker)

RN 432526-28-8 HCAPLUS

CN Benzoic acid, 3-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-

thiazolidinylidene]methyl}- (9CI) (CA INDEX NAME)



CC 1-12 (Pharmacology)

Section cross-reference(s): 14

IT 28600-65-9D, Thiazolidinone, derivative 432526-28-8

(altered channel gating mechanism for CFTR inhibition by
high-affinity thiazolidinone blocker)

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L9 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:524152 HCAPLUS Full-text

DOCUMENT NUMBER: 140:199242

TITLE: Synthesis and study of antimicrobial activity
of azolidine derivatives with
2-(2-chlorobenzyloxy)-5-nitrophenyl fragments
intercalated into molecules

AUTHOR(S): Lesik, R. B.; Zimenkovs'kii, B. S.; Kutsik, R.
V.; Atamanyuk, D. V.; Sementsiv, G. M.

CORPORATE SOURCE: L'viv. Derzhavnii Med. Univ. im. Danila
Galits'kogo, Lvov, Ukraine

SOURCE: Farmatsevtichnii Zhurnal (Kiev) (2003), (2),
52-56

CODEN: FRZKAP; ISSN: 0367-3057

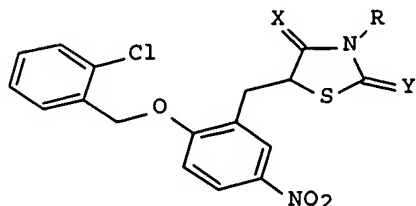
PUBLISHER: Zdorov'ya

DOCUMENT TYPE: Journal

LANGUAGE: Ukrainian

OTHER SOURCE(S): CASREACT 140:199242

GI



I

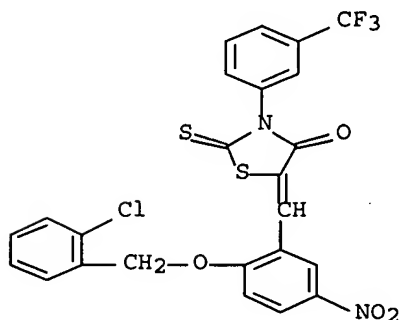
AB Combinatorial library of azolidine derivs. with 2-(2-chlorobenzoyloxy)-5-nitrophenyl fragment in mols., e.g. I [X = O, Y = S, R = H, 3-HOC₆H₄, HO₂CCH₂, 2-furylmethyl, etc.; X = Y = O, R = H; X = S, Y = O, R = H], has been synthesized using Knoevenagel condensation and hetero-Diels-Alder cycloaddn. I (X = O; Y = S; R = H) showed significant antimicrobial activity and was selected as the lead compound for search of potential antimicrobial compds. with thiazolidine template.

IT 501112-00-1P

(preparation and antimicrobial activity of
(chlorobenzoyloxy)nitrophenyl-substituted thiazolidinones,
imidazolidinones and fused derivs.)

RN 501112-00-1 HCAPLUS

CN 4-Thiazolidinone, 5-[[2-[(2-chlorophenyl)methoxy]-5-nitrophenyl]methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]-
(9CI) (CA INDEX NAME)



CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 10

IT 500203-06-5P 501111-99-5P 501112-00-1P 613218-83-0P
613218-85-2P 613218-87-4P 613218-90-9P 613218-92-1P
613219-07-1P 613219-18-4P 663605-35-4P 663605-36-5P

(preparation and antimicrobial activity of
(chlorobenzoyloxy)nitrophenyl-substituted thiazolidinones,
imidazolidinones and fused derivs.)

L9 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:932809 HCAPLUS Full-text

DOCUMENT NUMBER: 139:235

TITLE: Thiazolidinone CFTR inhibitor identified by
high-throughput screening blocks cholera
toxin-induced intestinal fluid secretion

AUTHOR(S): Ma, Tonghui; Thiagarajah, Jay R.; Yang, Hong;
Sonawane, Nitin D.; Folli, Chiara; Galletta,
Luis J. V.; Verkman, A. S.

CORPORATE SOURCE: Department of Medicine, Cardiovascular
Research Institute, University of California,
San Francisco, San Francisco, CA, 94143-0521,
USA

SOURCE: Journal of Clinical Investigation (2002),
110(11), 1651-1658

December, 2002

CODEN: JCINAO; ISSN: 0021-9738

PUBLISHER: American Society for Clinical Investigation

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Secretory diarrhea is the leading cause of infant death in developing countries and a major cause of morbidity in adults. The cystic fibrosis transmembrane conductance regulator (CFTR) protein is required for fluid secretion in the intestine and airways and, when defective, causes the lethal genetic disease cystic fibrosis. We screened 50,000 chemical diverse compds. for inhibition of cAMP/flavone-stimulated Cl⁻ transport in epithelial cells expressing CFTR. Six CFTR inhibitors of the 2-thioxo-4-thiazolidinone chemical class were identified. The most potent compound discovered by screening of structural analogs, CFTRinh-172, reversibly inhibited CFTR short-circuit current in less than 2 min in a voltage-independent manner with K_i approx. 300 nM. CFTRinh-172 was nontoxic at high concns. in cell culture and mouse models. At concns. fully inhibiting CFTR, CFTRinh-172 did not prevent elevation of cellular cAMP or inhibit non-CFTR Cl⁻ channels, multidrug resistance protein-1 (MDR-1), ATP-sensitive K⁺ channels, or a series of other transporters. A single i.p. injection of CFTRinh-172 (250 µg/kg) in mice reduced by more than 90% cholera toxin-induced fluid secretion in the small intestine over 6 h. Thiazolidinone CFTR inhibitors may be useful in developing large-animal models of cystic fibrosis and in reducing intestinal fluid loss in cholera and other secretory diarrheas.

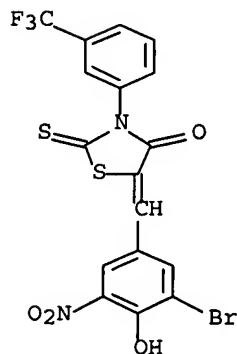
IT 292174-08-4 301308-44-1 303056-54-4

307510-92-5 328250-71-1 535962-72-2

(thiazolidinone CFTR inhibitor identified by high-throughput screening blocks cholera toxin-induced intestinal fluid secretion)

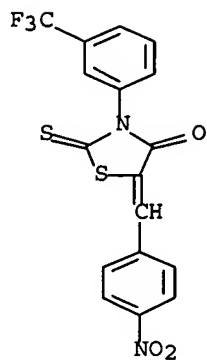
RN 292174-08-4 HCAPLUS

CN 4-Thiazolidinone, 5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



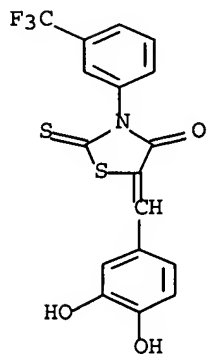
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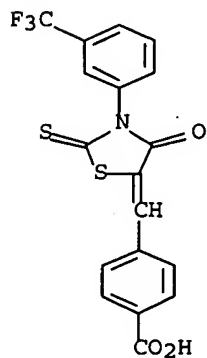
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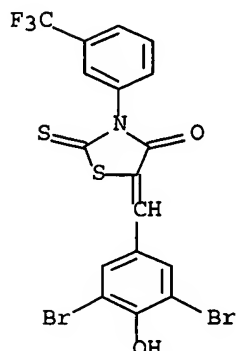


RN 307510-92-5 HCAPLUS

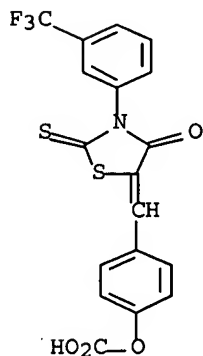
CN Benzoic acid, 4-[[4-oxo-2-thioxo-3-[3-(trifluoromethyl)phenyl]-5-thiazolidinylidene]methyl]- (9CI) (CA INDEX NAME)



RN 328250-71-1 HCAPLUS
CN 4-Thiazolidinone, 5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thio-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



RN 535962-72-2 HCAPLUS
CN 4-Thiazolidinone, 5-[[4-(carboxyoxo)phenyl)methylene]-2-thio-3-[3-(trifluoromethyl)phenyl]- (9CI) (CA INDEX NAME)



CC 1-1 (Pharmacology)
IT 141-84-4D, 2-Thio-4-thiazolidinone, derivs. 292174-08-4
301308-44-1 303056-54-4 307510-92-5
328250-71-1 535962-72-2
(thiazolidinone CFTR inhibitor identified by high-throughput
screening blocks cholera toxin-induced intestinal fluid
secretion)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

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FILE 'MARPAT' ENTERED AT 11:53:31 ON 31 OCT 2006
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FILE CONTENT: 1961-PRESENT VOL 145 ISS 18 (20061027/ED)

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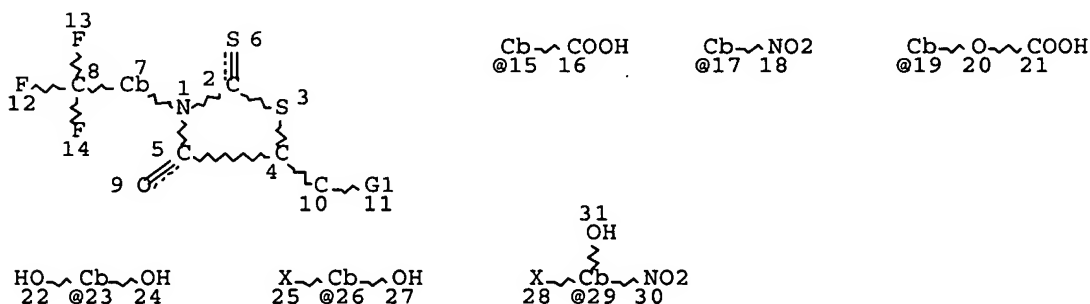
MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US 7108861 19 SEP 2006
DE 102006006123 07 SEP 2006
EP 1700848 13 SEP 2006
JP 2006242783 14 SEP 2006
WO 2006095864 14 SEP 2006
GB 2423518 30 AUG 2006
FR 2882520 01 SEP 2006
RU 2283369 10 SEP 2006
CA 2547866 22 AUG 2006

Expanded G-group definition display now available.

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OR 328250-71-1/BI OR 504-78-9/BI OR 50718-91-7/BI OR
535962-72-2/BI OR 619-66-9/BI OR 677027-74-6/BI OR
677027-75-7/BI OR 98-16-8/BI)
L3 STR



VAR G1=15/17/19/23/26/29

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DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 31

STEREO ATTRIBUTES: NONE

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L6 7 SEA FILE=REGISTRY ABB=ON L5 AND L2
L7 9 SEA FILE=HCAPLUS ABB=ON L6
L8 11 SEA FILE=HCAPLUS ABB=ON L5
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L12 6 SEA FILE=MARPAT ABB=ON L11 NOT L9

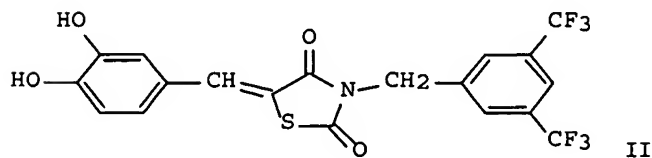
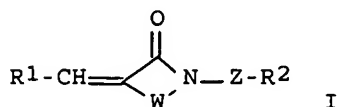
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L12 ANSWER 1 OF 6 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 142:336364 MARPAT Full-text
TITLE: Preparation of thiazolidinedione and
3,4-dihydropyrazol-3-ones as plasminogen
activator inhibitor-1 inhibitors
INVENTOR(S): Muto, Susumu; Kubo, Asako; Itai, Akiko;
Sotome, Tomomi; Yamaguchi, Yoichi
PATENT ASSIGNEE(S): Institute of Medicinal Molecular Design. Inc.,
Japan
SOURCE: PCT Int. Appl., 438 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005026127	A1	20050324	WO 2004-JP13193	20040903
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
EP 1666469	A1	20060607	EP 2004-772932	20040903
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR			

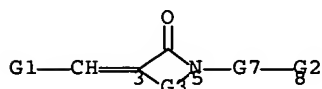
PRIORITY APPLN. INFO.: JP 2003-319191 20030911
WO 2004-JP13193 20040903

GI

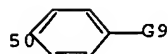


AB A medicine having plasminogen activator inhibitor-1 (PAI-1) inhibiting activity comprises as an active ingredient a compound of the general formula (I) [wherein R1, R2 = (un)substituted aromatic groups; W = a group selected from among linkage groups of formulas -X-C(:X)- and -C(R3):N- (wherein the left side bonds effect linkage with a carbon atom while the right side bonds effect linkage with a nitrogen atom; X = sulfur atom or NH; Y = oxygen or sulfur atom; R3 = a hydrocarbon group, hydroxyl, or carboxyl); Z = a single bond or a linkage group whose main chain has 1 to 3 atoms] or a salt thereof. This medicine is useful for the prevention and/or treatment of diseases caused by increased activity of PAI-1 or diseases caused by ≥ 2 of unusual states selected from thrombogenesis, fibrosis, organ fat accumulation, cell proliferation, angiogenesis, deposition or reconstruction of outer cellular matrix, and cell migration or metastasis. Thus, a mixture of 0.15 mmol 3,4-dihydroxybenzaldehyde, 0.15 mmol 3-[3,5-bis(trifluoromethyl)benzyl]thiazolidine-2,4-dione, and 4 mL toluene was treated with two drops of AcOH and two drops of piperidine and heated at 90° for 40 min to give 5-(3,4-dihydroxybenzylidene)-3-[3,5-bis(trifluoromethyl)benzyl]thiazolidine-2,4-dione (II). II at 25 μ M in vitro inhibited >99% inactivation of 2-chain tissue-type plasminogen activator (tPA) by human PAI-1.

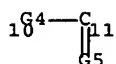
MSTR 1



G1 = Ph (substd. by G14)
G2 = 50



G3 = 10-3 11-5



G4 = S
G5 = S
G7 = bond
G9 = CF3
G14 = 1 or more CO2H

Patent location:

Note:

claim 1

and pharmacologically acceptable salts,
hydrates or solvates

REFERENCE COUNT:

9

THERE ARE 9 CITED REFERENCES AVAILABLE

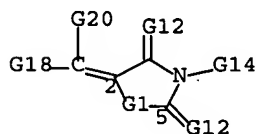
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L12 ANSWER 2 OF 6 MARPAT COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 142:256729 MARPAT Full-text
 TITLE: Screening proteases participating in
 heparanase activation, and pharmaceutical
 compns for medical uses
 INVENTOR(S): Gelder, Joel M.; Miron, Daphna
 PATENT ASSIGNEE(S): Insight Biopharmaceuticals Ltd., Israel
 SOURCE: U.S. Pat. Appl. Publ., 102 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

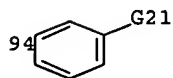
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005042213	A1	20050224	US 2004-916598	20040812
PRIORITY APPLN. INFO.:			US 2003-494800P	20030814
			US 2004-535492P	20040112

AB The current invention relates to methods for screening proteases participating in heparanase activation. The pharmaceutical compns. for modulating heparanase activation, i.e., inhibiting or accelerating heparanase activity and medical uses are also provided.

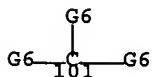
MSTR 2



G1 = S
 G6 = F
 G12 = O / S
 G14 = 94



G18 = Ph (opt. substd. by 1 or more G22)
 G21 = 101



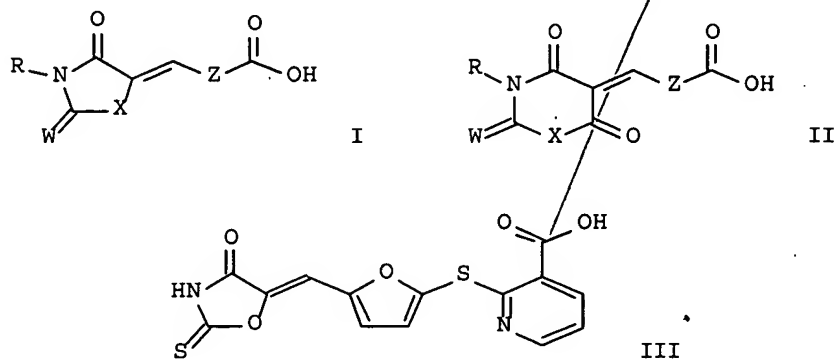
G22 = CO2H

Patent location: claim 27

L12 ANSWER 3 OF 6 MARPAT COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 139:276889 MARPAT Full-text
TITLE: Preparation of [(heterocyclyl)methylene]-
substituted benzoic acids and nicotinic acids
as antibacterials
INVENTOR(S): Leslie, Bruce W.; Allanson, Nigel M.; Grant,
Richard M.; Thomson, Samantha; Zhao, Lihua;
Woolley, J. Christopher; Davies, Rhian J.
PATENT ASSIGNEE(S): Pantherix Ltd, UK
SOURCE: Brit. UK Pat. Appl., 15 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2386892	A1	20031001	GB 2002-7410	20020328
PRIORITY APPLN. INFO.:			GB 2002-7410	20020328

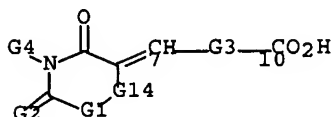
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AB General procedures for the preparation of title antibiotics I and II [wherein W = S or O; X = NH, S, or O; Z = one or more (un)substituted Ph or heterocyclyl rings optionally separated by a spacing group (Y)_n; R = H, (Y)_nCO₂H, or (un)substituted Ph or heterocyclyl ring optionally separated by a spacing group (Y)_n; Y = CH₂, O, NH, S, SO, or SO₂; n = 0-6] (no data) and intermediate aldehydes are presented. For example, 2-mercaptonicotinic acid was coupled with 5-bromo-2-furaldehyde in the presence of KOH in DMF to give 2-[(5-formylfuran-2-yl)thio]nicotinic acid (92%), which was condensed with the appropriate oxazolidine to afford III (no data). The latter inhibited the enzymic activity of Staphylococcus aureus phosphopantetheine adenylyltransferase (PPAT) with an IC₅₀ value of 0.68 μM. Thus, I and II and

their pharmaceutical compns. are useful for treatment of gram pos. bacterial infections.

MSTR 1



G1 = S
G2 = S
G3 = phenylene (opt. substd. by 1 or more G5)
G4 = Ph (opt. substd. by 1 or more G5)
G5 = CF3
G14 = bond

Patent location: claim 1

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L12 ANSWER 4 OF 6 MARPAT COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 136:232302 MARPAT Full-text

TITLE: Preparation of 1-phenyl-2,5-
imidazolidinediones and analogs for treatment
of inflammatory and immune cell-mediated
diseases

INVENTOR(S): Kelly, Terence A.; Bormann, Barbara Jean;
Frye, Leah Lynn; Wu, Jiang-Ping

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc.,
USA

SOURCE: U.S., 114 pp., Cont.-in-part of Appl. No.
PCT/US98/04254.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

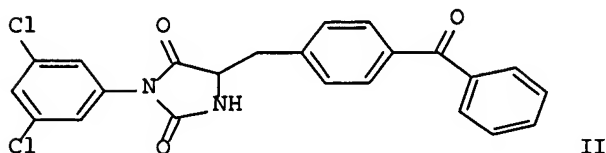
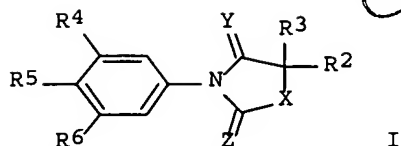
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6355664	B1	20020312	US 1999-375010	19990816
WO 9839303	A1	19980911	WO 1998-US4254	19980303
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 38132	E	20030603	US 2002-167732	20020612
PRIORITY APPLN. INFO.:				US 1997-40011P 19970303
				US 1998-33148 19980302

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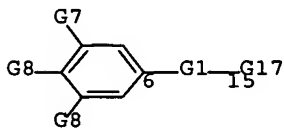
⊖ double bond



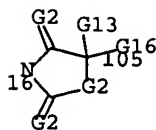
No

AB Title imidazolidinediones, pyrrolidinediones, oxazolidinediones, and thiazolidinediones I [wherein Y = O or S; Z = O or S; X = CHR1, NR1, CHSO2R1, or NSO2R1; R1 = H, carboxylic acid group, phosphonic acid group, sulfonic acid group, imidamidoalkyl, guanidinoalkyl, or (un)substituted (cyclo)alkyl, piperidyl, or aryl; R2 = H or (un)substituted (cyclo)alkyl; R3 = H or (un)substituted aryl(alkyl); R4 = Cl or CF3; R5 and R6 = independently H, halo, Me, or CF3; and pharmaceutically acceptable salts] were prepared as intracellular adhesion mols. (ICAMs) and leukointegrin antagonists. For example, reaction of 4-benzoyl-DL-phenylalanine with 3,5-dichlorophenylisocyanate and cyclization of the ureidoacetic acid intermediate gave II. The latter inhibited lymphocyte function-associated 1 (LFA-1) binding to ICAM-1 with Kd of 1.64 μ M. I are useful for the treatment of inflammatory and immune cell-mediated disorders, such as psoriasis, organ/tissue transplant rejection, graft vs. host reactions, autoimmune diseases, asthma, and toxicity associated with cytokine therapy.

MSTR 1



G1 = 16-6 105-15

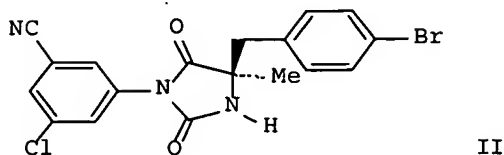
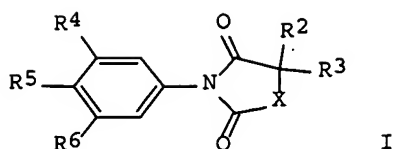


G2 = O / S
 G8 = CF3
 G16 = (0-2) CH2 (opt. substd.)
 G17 = Ph (opt. substd. by 1 or more G22)
 G22 = NO2
 Patent location: claim 1
 Note: or pharmaceutically acceptable salts
 Note: additional ring formation also claimed
 Note: also incorporates broader disclosure

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE
 FOR THIS RECORD. ALL CITATIONS AVAILABLE
 IN THE RE FORMAT

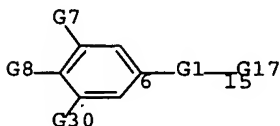
L12 ANSWER 5 OF 6 MARPAT COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 134:131534 MARPAT Full-text
 TITLE: Novel N-aryl nitrogen heterocyclic compounds
 useful in the treatment of inflammatory
 disease
 INVENTOR(S): Kelly, Terence Alfred; Sorcek, Ronald John
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc.,
 USA
 SOURCE: PCT Int. Appl., 101 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2001007044	A1	20010201	WO 2000-US17712	20000628
W: CA, JP, MX				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,				
MC, NL, PT, SE				
US 6353013	B1	20020305	US 2000-605574	20000628
PRIORITY APPLN. INFO.:			US 1999-144893P	19990721
GI				

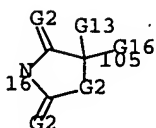


AB Novel N-aryl nitrogen heterocyclic compds. I [Y and Z are independently O or S; X = O, S, CHR₁, NR₁, CHSO₂R₁ or NSO₂R₁; R₁ = H, (un)substituted branched or unbranched alkyl, alkylcarboxylic acid, alkylphosphonic acid, alkylamidino, N-substituted piperidyl, etc.; R₂ = H, (un)substituted branched or unbranched alkyl or cycloalkyl; R₃ = (CR₇R₈)_x(CR₉R₁₀)_yR₁₁ where x and y independently = 0 or 1; R₇, R₈, and R₉ independently = H, OH, alkoxy, acyloxy, branched or unbranched alkyl or cycloalkyl; R₁₀ = H, OH, alkoxy, acyloxy, branched or unbranched alkyl or cycloalkyl, (un)substituted aryl; R₁₁ = (un)substituted aryl; R₄ = Cl, CF₃; R₅ = H, halo, Me, CF₃; R₆ = CN or NO₂] which are useful for treating or preventing inflammatory and immune cell-mediated diseases (no data) are disclosed as well as methods for their preparation. Thus, II was prepared by hydrolysis of 5-(R)-(4-bromobenzyl)-3-(5-acetamino-3-chlorophenyl)-5-methylimidazoline-2,4-dione followed by Sandmeyer reaction with NaNO₂, CuCN and KCN. Pharmaceutical compns. of I suitable for prevention or treatment of inflammatory and immune cell-mediated conditions are disclosed.

MSTR 1



G1 = 16-6 105-15



G2 = 0 / S
 G8 = CF3
 G16 = (0-2) CH2 (opt. substd.)
 G17 = Ph (opt. substd. by 1 or more G22)
 G22 = NO2
 Patent location: claim 1
 Note: or pharmaceutically acceptable salts
 Note: additional ring formation also claimed

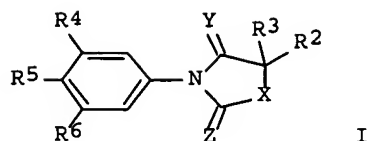
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE
 FOR THIS RECORD. ALL CITATIONS AVAILABLE
 IN THE RE FORMAT

L12 ANSWER 6 OF 6 MARPAT COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 129:260456 MARPAT Full-text
 TITLE: Small molecules useful in the treatment of
 inflammatory disease
 INVENTOR(S): Kelly, Terence Alfred; Bormann, Barbara Jean;
 Frye, Leah Lynn; Wu, Jiang-ping
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharmaceuticals, Inc.,
 USA
 SOURCE: PCT Int. Appl., 361 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

No double bond

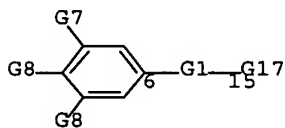
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9839303	A1	19980911	WO 1998-US4254	19980303
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2278547	AA	19980911	CA 1998-2278547	19980303
AU 9865418	A1	19980922	AU 1998-65418	19980303
EP 966447	A1	19991229	EP 1998-911475	19980303
EP 966447	B1	20030305		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EE 9900481	A	20000615	EE 1999-481	19980303
TR 9902124	T2	20000621	TR 1999-2124	19980303
BR 9811260	A	20000808	BR 1998-11260	19980303
JP 2001513821	T2	20010904	JP 1998-538772	19980303
AT 233738	E	20030315	AT 1998-911475	19980303
ES 2191286	T3	20030901	ES 1998-911475	19980303
ZA 9807065	A	20000207	ZA 1998-7065	19980806
US 6355664	B1	20020312	US 1999-375010	19990816
MX 9907583	A	20000228	MX 1999-7583	19990817
NO 9904256	A	19991102	NO 1999-4256	19990902
BG 103711	A	20010928	BG 1999-103711	19990902
US 38132	E	20030603	US 2002-167732	20020612
PRIORITY APPLN. INFO.:			US 1997-40011P	19970303
			US 1998-33148	19980302
			WO 1998-US4254	19980303

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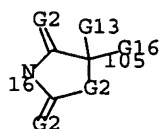


AB Title small mols. [I; Y = O, S; Z = O, S; X = CH₂, NH, CHSO₂H, etc.; R₂ = H, cycloalkyl, OH, etc.; R₃ = H, OH, alkyloxy, alkyl; R₄ = Cl, CF₃; R₅ = H, F, Cl, Br, I, CH₃, CF₃; R₆ = H, F, Cl, Br, I, CH₃, CF₃] and pharmaceutically acceptable salts are prepared A method treating or preventing inflammatory and immune cell-mediated diseases by the administration of certain novel and known small mols. such as (R)-I (X = NH; Y = O; Z = O; R₂ = CH₃; R₃ = 4-BrC₆H₄CH₂; R₄ = R₆ = Cl; R₅ = H).

MSTR 1



G1 = 16-6 105-15



G2 = O / S

G8 = CF₃G16 = (0-2) CH₂ (opt. substd.)

G17 = Ph (opt. substd. by 1 or more G22)

G22 = NO₂

Derivative:

or pharmaceutically acceptable salts

Patent location:

claim 1

Note:

additional ring formation also claimed

REFERENCE COUNT:

7

THERE ARE 7 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT